Think high-risk nmCRPC. Think referral. Think NUBEQA®.[1-4]

INDICATION

NUBEQA is indicated for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.[4]

ADT: androgen deprivation therapy; AE: Adverse event; AR: androgen receptor; MFS: metastasis free survival; nmCRPC: non-metastatic castration resistant prostate cancer; PSA: prostate specific antigen; OS: overall survival; QoL: quality of life.

*nmCRPC is defined as no evidence of metastatic disease, a rising PSA concentration and a PSA doubling time of ≤10 months.[1]

†Median MFS for NUBEQA + ADT was 40.4 months (n=955) and 18.4 months for placebo + ADT (n=554) (HR: 0.41; 95% CI: 0.34-0.50; p<0.001).[2] At 3 years, NUBEQA + ADT significantly reduced the risk of death by 31% vs. placebo + ADT (83% vs. 77%; HR: 0.69; 95% CI: 0.53-0.88; p=0.003).[3]

**Discontinuation due to AEs: 8.9% NUBEQA + ADT (n=954) vs. 8.7% placebo + ADT (n=554). Any AE: 83.2% NUBEQA + ADT (n=954) vs. 76.9% placebo + ADT (n=554). The most common AE with NUBEQA was fatigue (12.1%).[2]

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NUBEQA® ▼ (darolutamide) 300 mg tablets

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▼ NUBEQA® (Darolutamide) 300 mg film-coated tablets
Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)
Presentation: Each film-coated tablet contains 300 mg of darolutamide. **Indication(s):** NUBEQA is indicated for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease. **Posology & method of administration:** Treatment should be initiated and supervised by a specialist physician experienced in treatment of prostate cancer. Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated. For oral use. The tablets should be taken whole with food. ***Adults:*** 600 mg darolutamide (two tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1200 mg. ***Children & adolescents:*** There is no relevant use of darolutamide in the paediatric population for the indication of treatment of nmCRPC. ***Elderly:*** No dose adjustment is necessary. ***Renal Impairment:*** No dose adjustment is necessary for patients with mild or moderate renal impairment. For patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m²) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily. ***Hepatic Impairment:*** No dose adjustment is necessary for patients with mild hepatic impairment. The available data on darolutamide pharmacokinetics in moderate hepatic impairment is limited. Darolutamide has not been studied in patients with severe hepatic impairment. For patients with moderate and severe hepatic impairment (Child-Pugh Classes B and C), the recommended starting dose is 300 mg twice daily. **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients. Women who are or may become pregnant. **Warnings & precautions:** The available data in patients with severe renal impairment are limited. As exposure might be increased those patients should be closely monitored for adverse reactions. The available data in patients with moderate hepatic impairment are limited, and darolutamide has not been studied in patients with severe hepatic impairment. As exposure might be increased those patients should be closely monitored for adverse reactions. Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and symptomatic congestive heart failure were excluded from the clinical studies. Therefore, the safety of darolutamide in these patients has not been established. Use of strong CYP3A4 and P-gp inducers during treatment with darolutamide may decrease the plasma concentration of darolutamide and is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product with less potential to induce CYP3A4 or P-gp should be considered. Patients should be monitored for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates as co-administration with darolutamide may increase the plasma concentrations of these substrates. Co-administration with rosuvastatin should be avoided unless there is no therapeutic alternative. In patients with a history of risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating NUBEQA. NUBEQA 300mg film-coated tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicinal product. **Interactions:** For the effect of other medicinal products on the action darolutamide (e.g CYP3A4, P-gp inducers and CYP3A4, P-gp and BCRP inhibitors and UGT1A9 inhibitors) and the action of darolutamide on other medicinal products (BCRP, OATP1B1, OATP1B3 substrates, P-gp substrates, CYP3A4 substrates and other medicinal products that prolong the QT interval) refer to the SmPC. **Pregnancy & lactation:** Darolutamide is not indicated in women of childbearing potential, and it is not to be used in women who are, or may be, pregnant or breast-feeding. Unknown whether darolutamide or its metabolites are present in semen. If the patient is engaged in sexual activity with a woman of childbearing potential, a highly effective contraceptive method (<1% failure rate per year) should be used during and for 1 week after completion of treatment. Unknown whether darolutamide or its metabolites are excreted in human milk. No studies in animals have been conducted to evaluate the excretion of darolutamide or its metabolites into milk. A risk to the breast-fed child cannot be excluded. There are no human data on the effect of darolutamide on fertility. Based on animal studies, darolutamide may impair fertility in males of reproductive potential. **Effects on ability to drive and use machines:** Darolutamide has no or negligible influence on the ability to drive and use machines. **Undesirable effects:** *Very common:* fatigue/asthenic conditions (incl. fatigue and asthenia, lethargy and malaise), neutrophil count decreased, bilirubin increased, AST increased. *Common:* ischaemic heart disease (including arteriosclerosis coronary artery, coronary artery disease, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, acute myocardial infarction, angina pectoris, angina unstable, myocardial infarction, myocardial ischaemia), heart failure (including cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiogenic shock), rash, pain in extremity, musculoskeletal pain, fractures. Prescribers should consult the SmPC in relation to other side effects. **Overdose:** In the event of intake of a higher than recommended dose, treatment with darolutamide can be continued with the next dose as scheduled. There is no specific antidote for darolutamide and symptoms of overdose are not established. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** Pack of 112 film-coated tablets, £4,040. **MA Number(s):** EU/1/20/1432/001 **Further information available from:** Bayer plc, 400 South Oak Way, Reading RG2 6AD, United Kingdom. Telephone: 0118 206 3000. **Date of preparation:** March 2020

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Research Communication

A novel tattooing technique for ureteric strictures in robotic ureteroureterostomy: a non-inferiority analysis

A ureteric stricture can be treated either endoscopically or with ureteric reconstruction. The developments in robotic ureteric repair have led to similar success rates to open techniques, with the addition of decreased hospitalization duration and blood loss [1–7].

Recognition of the stricture during robotic ureteric reconstruction, however, can be challenging. In this study, we introduce the novel technique of ureteroscopic 'tattooing' of the ureteric lumen on the level of the stricture to subsequently recognize it during robotic ureteroureterostomy. We also compare our technique with others used for ureteric stricture identification. Our preliminary data show that this technique is easy to use and can reduce the operating time and the complication rate postoperatively.

A total of four patients with benign ureteric strictures underwent robot-assisted ureteroureterostomy in a single tertiary hospital. All patients underwent preoperative MAG3 renograms and CT urograms, which showed obstruction on the side of the stricture and provided a measure of its length (<3 cm). Patients were followed up for 1 year after their procedures with MAG3 renograms at 3 and 12 months. Three patients were male and one female. All the male patients had left ureteric strictures, while the female patient had a right stricture. Long standing obstruction from impacted ureteric stones caused the stricture in two patients and multiple ureteroscopies caused it in the other two. In all the cases a retrograde ureteroscopy with a semirigid 7-Fr ureteroscope preceded the robotic ureterectomy. A retrograde study confirmed the length of the stricture in all cases. The patients were placed in a Lloyd-Davies position. The distal end of the ureteric stricture was marked with black dye with the use of a fine endoscopic injection needle (EndoTNeedle™; GI Supply, Specialty Endoscopic Products, Mechanicsburg, PA, USA) through the working channel.

Initially, the needle was pushed through the mucosa. It is of utmost importance to approach the mucosa tangentially to avoid the injection of the dye outside the ureter, which can cause inflammation or the injury of surrounding organs and vessels. After insertion of the needle, the catheter was withdrawn slightly and pulled towards the lumen to ensure that the needle was directly under the mucosa. We inserted 0.5 mL of black dye on the anterior wall of the ureteric lumen (12 o' clock position) at the distal end of the stricture. We used a permanent carbon black dye, commercially available as Spot® Ex, ready for injection with the endoscopic injection needle. In all the cases we used the needle without the sheath to be able to pass it through the working channel of the ureteroscope.

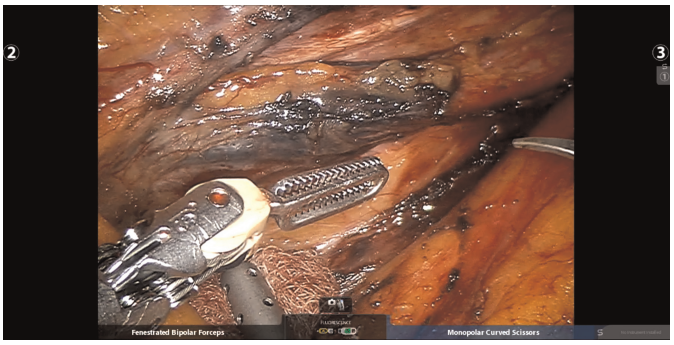
Subsequently the patient was placed in the supine position with the corresponding side of the operation elevated with a wedge. The Da Vinci Xi Robotic System was used with three robotic ports. The port configuration was similar to that used in robotic pyeloplasty.

The colon was mobilized and the marked 'tattooed' ureter was identified and mobilized extensively above and below the mark (Fig. 1). It was then incised just under the mark, opened, and 2–3 cm of ureteric segment above the mark were removed depending on the measured length of the stricture.

The proximal and distal ends are spatulated. A 3–0 double ended Quill-type suture was used for end-to-end anastomosis over a 6-Ch/26-cm JJ ureteric stent. Subsequently, an omental wrap was created and a 20-Fr Robinson's drain was placed next to the anastomosis.

All four patients in our study were discharged on the next day and no complications or readmissions occurred. The mean (range) operating time was 128.75 (110–150) min. The mean (range) blood loss was 45 (20–110) mL. The stent was removed 4 weeks later and a MAG3 renogram, performed at 3 months postoperatively, showed no obstruction, with improvement of the function of the kidney in three of the patients and unchanged function in the fourth patient (Table S1). The histology of the excised ureteric segment came back as benign in all patients. A subsequent MAG3 renogram at approximately 1 year after the procedure

Fig. 1 Identification of the 'tattooed' ureter during robotic ureterectomy and reconstruction. The distal end of the stricture has been marked endoscopically with black dye. Subsequently the segment of the ureter involving the stricture is removed proximal to the 'tattooed' part.



confirmed that the obstruction had resolved in all patients. No reactions or complications were observed that could be associated with the carbon black 'tattoo'.

Studies reporting ureter marking during robotic ureteroureterostomy were identified through three databases (PubMed, Cochrane and Medline). Non-English language and paediatric population studies were excluded during the initial screening. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed, with the following search terms used: 'robotic' OR 'robot' AND 'ureteral stricture' OR 'ureteral pathologies' OR 'ureteral reconstruction' OR 'upper urinary tract reconstruction'. Comparative outcomes (success and postoperative complications) and total and subgroup analyses were performed to identify whether ureter tattooing displayed favourable outcomes in comparison to particular marking techniques, which included simultaneous ureteroscopy, the use of intra-operative intraureteric indocyanine green (ICG) and intraureteric saline injection.

The search strategy identified 299 articles. Of these, 264 records were excluded during the initial screening process (not associated with the study, non-English language, paediatric), and another 28 were excluded at the full-text assessment (case reports, reviews, ureteric stricture identification technique not described). Finally, seven articles were included in this study for comparative analysis.

In five studies, simultaneous ureteroscopy was used to identify the stricture intra-operatively, while in the other two studies either ICG or saline is injected via a ureteric catheter during the robotic reconstruction.

Although the small number of patients did not allow statistically significant results, the preliminary data showed that our technique reduces the operating time of robotic ureteroureterostomy and demonstrates equal if not better success rates than the other techniques, with fewer complications, while also reducing the estimated blood loss and mean hospital stay. The mean follow-up period for our patients was shorter than that of other case series: 12 months vs 15 months.

Several techniques have been used to facilitate the recognition of ureteric strictures during robotic reconstruction, such as intraureteric injection of ICG. This requires the insertion of a ureteric catheter to perform the injection and the patient is placed in a modified lithotomy position during the robotic reconstruction. Also, ICG may spill outside the ureter upon incision, staining the field green and making it impossible to use intravascular ICG. Intra-operative ureteroscopy, performed to identify the ureteric obstruction by recognizing the light of the ureteroscope, requires the same patient positioning and a second surgeon to perform the ureteroscopy simultaneously with the reconstruction, as well as an extra monitor and stack with a light source [1–7].

Our technique of preoperative endoscopic 'tattooing' with the ureteroscope does not require the insertion of a ureteric catheter. The patient is in a preferred supine position during the robotic repair, and the simultaneous use of intravascular ICG to evaluate the ureter's viability is facilitated. No endoscopic instrumentation is required during the robotic reconstruction.

Although our technique is unique for robotic identification of ureteric strictures, the use of ureteric tattooing has been documented recently in patients undergoing ileal conduit diversion for future endoscopic ureteroenteric anastomoses identification [8].

The main limitations of our study are the small number of patients and the short follow-up period, which were not sufficient to fully evaluate the long-term results of our marking technique.

In conclusion, the preoperative ureteroscopic 'tattooing' of a ureteric stricture, performed to simplify its intra-operative identification during robotic ureteroureterostomy, is a novel marking technique, with promising safety and reliability outcomes. Larger series of patients followed up for a longer period of time are required to verify the effectiveness of this technique.

Conflict of Interest

None declared.

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Abbreviation: ICG, indocyanine green.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Postoperative results of MAG3 renograms after robotic ureteroureterostomy at 3- and 12-month follow-up appointments.